INTRODUCTION
Chapter 1  

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1. Introduction

For the past five thousand years, mankind has relied on natural products as the primary sources for medicines (Suffredini et al., 1999). However, the last two centuries have brought an explosion of understanding how these natural products are produced and how they interact with other organisms. Now at the start of a new millennium, it is estimated by the World Health Organization that, 80% of the world’s inhabitants must rely on traditional medicines for health care and these traditional medicines are primarily plant-based. It is estimated that 25% of all prescriptions dispensed in INDIA contained a plant extract or active ingredients derived from plants. All of these investigations demonstrate the importance of natural products in drug discovery.

Traditionally, peptic ulcers have been described as an imbalance between the luminal acid peptic attack versus the mucosal defense (Mutra et al., 1996). The treatment of peptic ulcers with plant products used in folk medicine and the protection of induced gastric ulcer in laboratory animals using medicinal plants was reported (Ahmad M. Disi et al., 1998). Generally plant flavonoids have been found to be effective against ulcer in experimental animals (David A. Lewis et al., 1999) and exhibit several biological effects (Rajnarayana et al., 2001).

1.1. Epidemiology

Gastric and duodenal ulcers have overlapping epidemiologic and pathophysiologic features, but they have significant differences. Duodenal ulcer patients have a younger age of onset and on average have increased parietal cell mass and acid secretion. Gastric ulcer patients have normal or decreased acid secretion, which is often associated with decreased mucosal defense. (Mertz HR et al., 1991) In the USA, about 10% of adults have peptic ulcer disease. Although incidence information in the elderly is limited, hospitalization, morbidity, and mortality rates from peptic ulcer disease are higher for the elderly than for the general population. High gastric ulcers tend to be large, tend to heal slowly and may be more prone to recur. Duodenal ulcers are more common than gastric ulcers.( The Merck Manual of
Geriatrics) According to study in Australia, up to 10% of the population will develop peptic ulcer disease at sometime in their lives. (Kamenka C et al., 2000)

1.2. Etiology:

- A peptic ulcer is a mucosal break, 3 mm or greater, that can involve the stomach or duodenum.
- The most important contributing factors are H pylori, NSAIDs, acid, and pepsin.
- Additional aggressive factors include smoking, ethanol, bile acids, aspirin, steroids, and stress.
- Important protective factors are mucus, bicarbonate, mucosal blood flow, prostaglandins, hydrophobic layer, and epithelial renewal.
- Increased risk when older than 50 d/t decrease protection
- When an imbalance occurs, PUD might develop.

1.3. Gastro duodenal Physiology:

Food after mastication is swallowed into the stomach after passing through the oesophagus. The stomach stores, mixes and empties the chyme into the duodenum for digestion and absorption into the small intestine. The secretion of HCl, pepsin, gastrin, intrinsic factor and mucus in stomach helps in digestion of proteins mainly. The parietal cells are responsible for secretion of HCl and maintenance of acidic pH of stomach ranging from 1-2 reaching up to 6-7. The gastric epithelium is constantly exposed to acids/pepsin/bile salts in addition to exogenous medications, bacteria and alcohol. Thus, a powerful defensive mechanism is required. This is provided by mucus bicarbonate layer which serves as a mucus gel impeding diffusion of harmful substances. A net imbalance in mucosal offensive and defensive factors play a major role in ulcer production. (Goel and Bhattacharia, 1991). Surface epithelial cells provide the next line of defence including mucus production, maintenance of pH and bicarbonate production. Any breach in pre epithelial barrier will cause migration of gastric epithelial cells to help in restitution. An alkaline pH and growth factors help in
restitution. Epithelial cell regeneration is regulated by Prostaglandins (PG) and growth factors (GF). An adequate oxygen and uninterrupted blood supply is essential which is provided by angiogenesis activated by GF. PG plays a central role in providing this defence (Valle et al., 2010).

1.4. INTRODUCTION TO PEPTIC ULCER

1.4.1. Peptic ulcers:
A peptic ulcer, also known as ulcus pepticum, PUD or peptic ulcer disease, is a mucosal erosion equal to or greater than 0.5 cm of an area in the stomach or duodenum. As many as 80% of ulcers are associated with Helicobacter pylori. Duodenal ulcers are generally benign but about 4% of gastric ulcers can be due to cancer. H. pylori was responsible for PU and not stress or spices as was commonly believed (Marsh, 1983, Marshal and Warren 1984). They won a Nobel Prize in 2005 on this discovery in Stockholm.

Morphologic features of H. pylori and NSAID-associated gastritis and gastric mucosal damage

- H. pylori
  - Extradigestive manifestations
  - Chronic active gastritis
  - Duodenal ulcer
  - Gastric ulcer
  - Gastric cancer
  - MALT lymphoma
  - Lower esophageal disease

- NSAIDs
  - Acute focal erosions
  - Capillary damage
  - Extravasation
  - Chronic inflammatory cells
  - Epithelial damage

Fig 1 Morphologic features of H. Pylori and NSAID-associated gastritis.
NSAIDS are mostly used all around the world. In the US over 100 million prescriptions are sold yearly. Thus, the drug related complications due to NSAIDS are most common. The toxicity of NSAIDS is due to inhibition of COX-1 isoform resulting in ulceration. Selective COX-2 inhibitors have an increased risk of myocardial infarctions. Aspirin, by reducing Prostaglandins (PG), are responsible for peptic ulcers. These drugs used in a short period of time are not typically dangerous but regular use can lead to gastritis (Siegelbaum, 2006). Other risk factors include cigarette smoking and alcohol consumption. Tobacco smoking leads to atherosclerosis and vascular spasms, causing vascular insufficiency and promoting the development of ulcers. Nicotine increases the secretion of histamine and gastrin by stimulating the enterochromaffin and G cells. Spicy foods also play a minor role in the development of peptic ulcers. O-blood groups are also prone to ulcers. Alcohol consumption erode the mucosal lining of the stomach. Low doses of alcohol stimulate hydrochloric acid secretion but high doses of alcohol do not stimulate secretion of acid (Wolff, 1989). Stress is a possible cause of ulcers. The Academy of Behavioral Medicine Research concluded that psychological factors play a significant role. Stress might promote \textit{H. pylori} infection by increase in gastric acidic secretion (Kim et al., 2002). Chronic stress was strongly associated with an increased risk of peptic ulcer (Wachirawat et al., 2003) About four million people suffer from peptic ulcer in the United States. About 3000 deaths/year are due to PUD in the USA. A relative increase in the incidence of duodenal ulcers is reported (Nimmo and Ford, 1978). There is a slight male preponderance with 0.05% of GU in males and 0.04% in females (Grossman, 1975). The prevalence of \textit{H. Pylori} infection in Western countries roughly matches according to age (20% at 20 years of age, 30% at30 and 80% at 80 years). Prevalence is higher in the third world. The life time risk of developing PU is 10% (Snowdex, 2008). Most of the synthetic preparations used in the treatment of ulcers have limitations. Thus a search for herbal products has been increased specially in the last decade. (Baquar, et al 1989). PUD are either \textit{H pylori} mediated (Goodwin et al., 1986; Konturek et al., 1999) or due to hypersecretion of acids due related to stress (Miller, 1987; Cook et al., 1991) and due to ingestion of
NSAID (Ivey, 1988; Langman et al., 1991). Treatment lies in controlling hypersecretion of acids by proton pump inhibitors and eradication of H. pylori. Caving of oxygen radicals and blocking of apoptosis further promote ulcer healing. Omeperazole provided this effect has thus been used extensively. Ranitidine, though useful had several side effects. Thus the use of non toxic plant products is currently gaining popularity.

**Dudodenal Peptic Ulcers:**

**Gastric Peptic Ulcers:**

Up until fairly recently, it was usual for a lecturer of gastroenterology to say, "we know little more than we did one hundred years ago about the cause and treatment of peptic ulcer disease." Actually, there have been notable and significant advances with regard to etiology, pathogenesis, pathophysiology, and biochemistry of this disease, as well as what might prove to be dramatic advances in medical management (Chapman ML et al., 1978) Modern therapy is extraordinarily effective in the management of gastric and duodenal ulcers, like Black's Nobel Prize for creating H2 blockers. Such success, however, make doctors assume that every ulcer is caused by excess acid. But the bismuth compounds and antibiotics also speed the healing of ulcers; some remain unconvinced that every peptic ulcer is caused by Helicobacter pylori because of the very ubiquity of that alien invader. However, it may be equally simple to deem all ulcers the product of excess acid. Indeed, different comments were on "heterogeneity" of peptic ulcer, to suggest that
craters have different causes. Some, like those of the Zollinger-Ellison syndrome, was clearly erosions from a torrent of hydrochloric acid. In some patients with arthritis, the defenseless mucosa is deprived of its protective prostaglandins inhibited by an excess of anti-inflammatory agents; the growing incidence of peptic ulcer in older women attest to that. The gastric ulcers turning up in young "crack" smokers tell of the ischemic origin of yet other ulcer. Some ulcer may even be the result of "stress". In any event, growing agreement that "peptic ulcers" are multifactorial in origin means that there is no more reason to think that an ulcer crater signifies a specific disease. (Spiro HM et al., 1991)

1.4.2. The Stomach

The stomach, once called the seat of the soul and still a recognized source of ecstasy and grief is one of the most metabolically active organ of the body. The stomach contributes in many ways to the complex adaptatics of the human being, from its decisive acceptance or rejection of food to its indispensable contribution to the production of red blood cells. (Stewart Wolf et al., 1965)

Fig 3 Bleeding perforation of Peptic ulcers
1.4.3. Physiology of Stomach

The stomach is a 'J' shaped organ which lies between the oesophagus and the duodenum. It has two curvatures namely, the lesser curvature and the greater curvature. It is composed of two units:
1. Fundus and Body.
2. Pyloric region.

There are three different types of gastric glands viz.
a. The cardiac glands.
b. Fundus and Body glands.
c. Pyloric glands.

The peptic cells, mucoid cells and parietal or oxyntic cells belong to the fundus and body glands. The peptic or chief cells secrete pepsinogen which is converted to pepsin at pH 1.8 in the gastric lumen. The mucoid cells secrete mucin which is a high molecular weight glycoprotein. These mucoid secretions have properties of adhesion, cohesion and high viscosity. The parietal cells secrete hydrochloric acid.

1.4.4. Composition of Gastric Juice

The gastric juice is composed of solid (0.56%) and water (99.44%). The solids include many organic substances like mucin, intrinsic factor, enzymes like pepsin, rennin and lipase. The inorganic constituents like Na+, Cl-, KCl, CaCl2 and HCl (0.4-0.5%) are present in the water portion.

1.5. Pathophysiology

Peptic ulcer disease is an excoriated segment of the gastrointestinal mucosa, typically in the stomach (gastric ulcer) or first few centimeters of the duodenum (duodenal ulcer), which penetrates through the muscularis mucosae. The pathophysiology of peptic ulcer is best viewed as an imbalance between mucosal defense factors (bicarbonate, mucin, prostaglandin, nitric oxide, other peptides and growth factors) and injurious factors (acid and pepsin). On average, patients with duodenal ulcers produce more acid than do control subjects particularly at night.
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(basal secretion). Although, patients with gastric ulcer have normal or even diminished acid production, ulcers are rare if ever occur in the complete absence of acid. Presumably, a weakened mucosal defense and reduced bicarbonate production on rebate to the injury from the relatively lower levels of acid in these patients. *H. pylori* and exogenous agents such as non-steroidal anti-inflammatory drugs (NSAIDs) interact in complex ways to cause an ulcer.( Brunton LL et al., 2006)

![Fig 4 Pathogenesis of Peptic Ulcer](image)

It is possible to divide peptic ulcers into three etiologic groups: those due to massive acid peptic hypersecretion in the Zollinger-Ellison syndrome; those due to nonsteroidal anti-inflammatory drugs (NSAIDs); and ulcers associated with *Helicobacter pylori* infection. *H.pylori* related ulcers forms the largest and least well understood subset of ulcer disease. Normal control of acid secretion depends on endocrine (gastrin), neural (vagal cholinergic nerves), and paracrine (histamine) limbs. Ingestion of meal causes increased acid and pepsin secretion due to an
increase in gastrin release and vagally mediated gastrin release is inhibited and acid secretion returns to baseline. Pepsinogen is secreted from the chief cell in response to gastrine and histamine. In the presence of acid, pepsinogen is elevated to pepsin, which is active at pH less than 4. It has been shown that acid is much more damaging to intestinal mucosa in the presence of pepsinogens (Kamenka C et al., 2000).

Fig 5 Mechanism of Gastric secretion
1.6. MECHANISM OF GASTRIC SECRETION :
(Men guy R. et al., 1997)

It is classified into:
1. Vagal-Antral Phase.
2. Intestinal Phase.

1. Vagal Antral Phase:
The sight, thought, smell or taste of food provokes a secretory response. An appetizing meal, result in secretion of large amounts of acid. Secretion occurs either by direct stimulation of the cells via cholinergic stimulation or by direct stimulation of the acid secreting cells which is mediated by a hormone called gastrin. Stomach secretes small amount of pepsinogen. However, the output of pepsin is enhanced with stimuli like histamine.

2. Intestinal phase:
Secretory activity reaches a peak during each meal and then wanes. The continuous interdigestive acid secretion is under the influence of the intestinal phase of gastric secretion.

The regulation of acid secretion by parietal cells:
The regulation of acid secretion by parietal cells is especially important in peptic ulcer and constitutes a particular target for drug action. The secretion of the parietal cells is an isotonic solution of HCl (150 mmol/l) with a pH less than 1, the concentration of H+ being more than a million times higher than that of plasma. The Cl⁻ is actively transported into canaliculi in the cells which communicate with lumen of the stomach. This Cl⁻ secretion is accompanied by K⁺, which is then exchanged for H⁺ from within cell by a K⁺/H⁺-ATPase. Carbonic anhydrase catalyses the combination of carbon dioxide and water to give carbonic acid which dissociates into H⁺ and bicarbonate ion( Rang HP et al., 2003) HCO₃⁻ diffuses into nearby blood capillaries. This “alkaline tide” of bicarbonate ions entering the blood stream after a meal may be large enough to elevate blood pH highly and make urine more alkaline.
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(Tortora GJ et al., 2006) Three main stimuli act on the parietal cells
1. Gastrin (a hormone)
2. Acetyl choline (a neurotransmitter)
3. Histamine (a local hormone).

Out of the three physiological secretagogues, histamine, acting through H2 receptors plays the dominant role because the other two, gastrin and Ach act partly directly and partly indirectly by releasing histamine from paracrine enterochromaffin like cells called “histaminocytes” located in the oxyntic glands (Tripathi KD et al., 1994).

Prostaglandins have been ascribed a “cytoprotective” role in the gastric mucosa by augmenting mucus & bicarbonate secretion, as well as other actions. PGE2, produced by gastric mucosa, inhibits acid secretion by opposing cAMP generation (in parietal cells) & gastrin release (from antral cells) (Tortora GJ et al., 2006)

1.7. FACTORS PRODUCING ULCERATION IN THE STOMACH:

(Fiasse R et al., 1970), (Lewis DA et al., 1987)

Factors producing ulceration are divided into three groups viz.

1. General factors.
2. Constitutional & environmental factors.
3. Local factors in the stomach.
1. General Factors: Vagal effects, hormonal effects (Histamine & Epinephrine), insufficient circulation, shock and general ischaemia etc.

2. Constitutional & environmental factors: Sex, age, family history, social class, geographical difference, occupation.

3. Local factors in the stomach:
   Aggressive factors: Hydrochloric acid, pepsin, refluxed bile, NSAID's, alcohol, pancreatic proteolytic enzymes, ingested irritants, bacterial toxins, physiochemical trauma. Defensive factors: Mucus, bicarbonates, blood flow, and restitution of epithelium. Factors involved in the development of chronic peptic ulcer which alter the balance between aggressive factors and defensive factors are as follows:
1. **Gastric hypersecretion & mucus and cellular turnover:**

Increased amount of acid and pepsin in higher concentration is supposed to be the basic cause of ulcer. The usual cause of peptic ulceration is too much secretion of gastric juice in relation to the degree of protection afforded to the mucosa by the mucus. Pure gastric juice is capable of destroying and digesting all living tissues including stomach. In the absence of extraneous stimuli, the human stomach secretes acid at a low rate. The parietal and chief cells secrete hydrochloric acid and pepsin which is a proteolytic enzyme. This proteolytic activity of pepsin in an acid medium carries the risk for the mucus membrane of gastrointestinal tract (Sodeman WA. *et al.*, 1967). The gastric mucosal barrier is broken down by many compounds like acids in high concentration, aliphatic acids, detergents, ethanol in high concentration 10%, salicylic acid and aspirin. Mucosal permeability is increased with high concentration of the above compounds which causes free access of acid to the gastric mucosa which causes ulceration. Alkaline mucus is the first line defense for gastric mucosa and it acts as a protective barrier. Mucus is a mixture of glycoprotein, water, serum and cellular macromolecules. Its capacity to protect the gastric mucosa is due to the presence of glycoprotein mucin which is secreted by mucus cells. The protection afforded by this layer is partly mechanical by preventing the access of acid and pepsin to the epithelial cells and partly chemical because it can neutralize the acid (Magee DF *et al.*, 1962). (Emanuel R; *et al.*, 1988) when the gastric epithelium is damaged, the mucus secretion is reduced. The mucosa then gets engorged. The slightest injury brings about hemorrhagic spots and erosions.

Mucus secretion is stimulated by mechanical contact with food. On contact with drugs, there is vigorous mucus secretion, followed by de-squamation of the surface cells. Repeated insult exhausts the ability to secrete mucus. The superficial layer of gastric mucosa renews itself every 2-3 days, so that any minor breaks in the mucosa are rapidly healed under normal circumstances. Alteration in the rate of cell renewal in upper elementary mucosa may account for progression of ulcer from acute to chronic. In addition to mucus protection, the duodenum is protected by the alkalinity of small intestinal secretions. Especially important is pancreatic secretions which
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contain large quantity of sodium bicarbonate which neutralizes the hydrochloric acid of gastric juice thus inactivating the pepsin to prevent the digestion of the mucosa.

2. Inflammatory Change:
Gastritis precedes the development of the ulcer. Inflammation causes the development of ulcer by altering the resistance of mucosa to digestion.

3. Bile Reflux:
The increased concentration of bile salts in stomach interferes with the integrity of gastric mucosa thus, predisposing to the development of ulceration.

4. Blood Supply:
Resistance of mucosa to digestion is reduced as a result of impaired blood supply. Such impairment could occur as a result of venous or arterial thrombosis or because of 'shunting' of blood within the mucosa.

5. Heredity:
A strong family history is frequently found in patients who develop ulcer in childhood or adolescence. There is an association between duodenal ulcer and blood group 'O'.

6. Sex Incidence:
Duodenal ulcers occur 5-10 times more often in men than in women and the perforation is 20 times more often in men. Although, these effects may be due to differences in life pattern of men and women, there are grounds for supposing that female sex hormones are in some way protective against peptic ulcer (Jain SM and Santani DD et al., 1994)

7. Stress:
There is undoubted association between development of acute ulcers in stomach or duodenum and physical or mental trauma or surgical operations.

8. Diet:
Absence of protective factors like fibres in the diet causes peptic ulcer. Janz & Beunting (1983) suggested that accumulation of Histamine and Tyramine in food by microbial action and their concentration in various food, wine, beer, fermented products also cause hyperacidity and ulceration.
9. Drugs:
Drugs like Phenylbutazone, Aspirin, Indomethacin, Cortisone and Reserpine are reported to cause ulcers.

10. Habit:
The incidence of ulceration is more in persons that are habituated to drink alcoholic beverages and tobacco smoking.

11. Constitutional factors:
There is sexual difference in occurrence of peptic ulcer. Peptic ulcer occurs at all ages in men. The incidence is very high (80%) in men compared to women. Ulcers are rare in women during the reproductive age and particularly during pregnancy. Ulcers may occur in women after menopause.

12. Occupation:
Duodenal ulcers are found to be more common among the physicians and business executives than among other professionals. The incidence is low in agricultural labourers. Other factors responsible for ulceration are chronic lung diseases, chronic liver diseases and hyperparathyroidism. Number of parietal cells present in stomach and hydrochloric acid secretion plays important/significant role in ulcer formation. Latest information suggests the role of bacterial organism, *Helicobacter pylori* which colonize the gastric mucosa, particularly the antral region in the development of chronic ulceration.

**Role of *H. pylori* in Infection:**

*H. pylorus* is a major etiological factor in peptic ulcer disease. About 95% of patients with duodenal ulcers and perhaps 80% of patients with gastric ulcers are infected with this bacterium and its eradication greatly diminishes the recurrence of these ulcers. *Helicobacter pylori* are a gram negative spiral bacterium that is found in patchy/distribution overlying the gastric epithelium. It was formerly named as *Campylobacter pylori* organism. *H. pylori* is a gram negative bacterium with the presence of sheathed flagella which gives motility, an external glycocalyx, major isoprenoid quinone being menaquinone-6 and a G+C content of chromosomal DNA of 35-44 mole %. *H. pylori* organisms have strong capability of urease production.
The bacteria then splits urease into urea and the NH3 thus released may become cause of increased acidity and hence enabling organism to survive. The released ammonia may be cytotoxic.
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Fig 7 Mechanism of Peptic Ulceration, gastric injury and protection. This diagram illustrates the progression from more mild forms of injury to ulceration that may occur with acute or chronic gastritis. Ulcers include layers of necrosis (N), inflammation (I), and granulation tissue (G), but a fibrotic scar (S), which takes time to develop, is only present in chronic lesions.
1.8. TREATMENT ASPECT FOR PEPTIC ULCER:

The treatments mentioned in various sources for Peptic Ulcer includes the following list. But one should always seek professional medical advice about any treatment or change in treatment plans.

1.8.1. Principles of peptic ulcer therapy:

As the exact cause of ulcer is not known, therapy is still empirical. It consists of:-

- Controlling gastric acidity, hypermotility and spasm and thus relieving the associated pain.
- Promoting ulcer healing.
- Prevention of complication and recurrence.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Common side effect</th>
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<tbody>
<tr>
<td>Antacid</td>
<td>Neutralize acid</td>
<td>Mg - diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Al - constipation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ca - constipation</td>
</tr>
<tr>
<td>H2 receptor antagonists</td>
<td>Block histamine receptor</td>
<td>Cytochrome 450 altered metabolism of drugs</td>
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<tr>
<td>Prostaglandins</td>
<td>Agonist</td>
<td>Diarrhea, cramps, abortion</td>
</tr>
<tr>
<td>H+/K+ATPase inhibitors</td>
<td>Block acid pump</td>
<td>Hypergastrinemia</td>
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<tr>
<td></td>
<td></td>
<td>enterochromaffin cell (ECL) hyperplasia</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>Coat ulcerated mucosa</td>
<td>Constipation</td>
</tr>
</tbody>
</table>

Fig 8 Anti Ulcer Drugs and their side effects

Gastric and duodenal ulcer, or peptic ulcer disease (PUD), Zollinger- Ellison's syndrome (ZES) and gastroesophageal reflex disease (GRD) are upper gastrointestinal disorders sharing a common abnormality: too much acid and pepsin activity for the degree of local tissue resistance. Therapy for these disorders is directed at correction of an apparent imbalance between acid and pepsin activity and
mucosal resistance. Success of therapy is measured in terms of symptom control, ulcer healing, relapse rate and the prevention of complications secondary to the disease and its treatment. The development of agents for the therapy of peptic ulceration has been a major pharmaceutical success story. The exciting era of the development of specific anti-ulcer therapy began with the observations of the workers in the laboratories of Smithkline and French and Welwyn-Garden city outside London and culminated in the development of new series of drugs termed H2-receptor antagonists, representing classical and rational pharmacological approach. Thus, Cimetidine and later Ranitidine revolutionized the treatment of peptic ulcers, with H2-receptor antagonists being the most widely used and effective novel drugs over the past decade. However, relapse ulceration following cessation of treatment with such agents is a frequent clinical observation. It is against this background that we have to deal with the current status and future advances in drug developments for the therapy of gastrointestinal ulceration. The stomach is constantly exposed to a variety of irritating and damaging factors, including its own acid pepsin secretion, bile, spicy foods, micro-organisms, alcohol and drugs. Despite this hostile environment, the gastric mucosa is usually capable of maintaining its integrity due to several protective mechanisms which include (1) mucus/alkaline secretion that adheres to the surface of the epithelium and exhibits a pH gradient within the unstirred water layer; (2) the gastric mucosal barrier preventing the penetration of acid into the mucosa; (3) rapid epithelial cell renewal allowing for a quick recovery from the mucosal insults; (4) rich mucosal blood flow providing oxygen and necessary nutrients to increased cellular resistance; and (5) the presence of natural humoral factors, particularly certain prostaglandins whose action may explain various aspects of mucosal protection. It is interesting to see how some of these natural protective mechanisms have been replicated or activated by exogenous means to treat the underlying peptic ulcer disease. Currently, drugs are available that may neutralise gastric acid, reduce gastric acid secretion, or enhance mucosal defences through "cytoprotective" or possible antimicrobial activities.
1.8.2. Antisecretory Agents:

The usual therapeutic approach towards the treatment of peptic ulcer disease is to reduce gastric acid by antacids and antisecretory drugs (anticholinergics, H2 blockers) or even acid reducing gastric surgery. Hydrochloric acid is secreted by the parietal cells under strict hormonal control. There are at least three major routes of parietal cell activation: vagal, histaminergic and gastrinergic. The earliest drugs that partially inhibited secretion depended on their ability to block the muscarinic receptor. The major problem with these type of drugs (e.g. atropine) was relative lack of efficacy and uncomfortable side effects. The currently used drug from this class,
1.8.3. H2 antagonists:

H2 antagonists are capable of over 90% reduction in basal, food stimulated, and nocturnal secretion of gastric acid after a single dose. These drugs also block the acid secretion stimulated by histamine, gastrin, cholinomimetic drugs and vagal stimulation. Histamine antagonists prevent occurrence of stress induced ulcers. However, their use in combination with antacids may be preferred. In addition, they are important in the medical management of ZES and gastric hypersecretory states seen in systemic mastocytosis. These drugs include mainly Cimetidine, **Ranitidine**, Famotidine and Nizatidine, Zaltidine, Mifentidine. TZU-0460, CM-57755 etc. are also under investigation and have shown better antiulcer activity. H+/K+ - ATPase as target for antisecretory drugs: Omeprazole represents this new class of gastric acid secretion inhibitors whose action can be described to the highly specific inhibitory action on gastric proton pump. Blockade of this pump constitutes a more direct
mechanism for acid secretion inhibition compared to blockade of histamine and cholinergic receptors. Omeprazole is not the active inhibitor of H+/K+ ATPase enzyme but is reversibly transformed in acidic media to the Sulfonamide, which can react with thiols to form disulfides, thus representing a model for the covalently linked enzyme-drug complex. The drug appears to require activation in the acid environment of the secretory canaliculus of the parietal cell i.e. it is a prodrug and probably acts from the external side of the membrane. NC-1300, RO 18-5362, B831-56 are series of fluorinated benzimidazoles and are potent and long lasting inhibitors of acid secretion in animals and have shown mechanism similar to that of Omeprazole.

1.8.4. Cytoprotective Agents:
In 1968, Robert recognized that prostaglandins (PGs) inhibit gastric acid secretion and protect against experimental ulcers. According to (Robert et al.), cytoprotection refers to protection against chemically (e.g. concentrated ethanol, acid or base) or physically (e.g. heat) induced hemorrhagic acute gastric erosions and ulcer by prostaglandins in doses much smaller than those needed to reduce gastric secretion.
in the rat. Histological investigations revealed that only the deep hemorrhagic necrosis is prevented whereas the surface cell injury is not decreased by so-called protective compounds. The mechanism for such gastroprotection by prostaglandins has not been clearly defined but some theories have been proposed:

**a) Prevention of gastric barrier disruption:**
Prostaglandins prevent disruption of the gastric mucosa from barrier breakers like Aspirin, Indomethacin, Ethanol and Bile salts etc. Disruption of the barrier allows hydrogen ions to diffuse from the gastric lumen back into the mucosa and sodium and potassium ions to diffuse from the mucosa into the gastric lumen. Barrier disruption can cause gastric mucosal damage and bleeding into the gastric lumen.

**b) Stimulation of gastric protectors:**
Prostaglandins stimulate the formation of gastric mucus and nonparietal cell alkaline secretion rich in sodium and chloride ions and in bicarbonate. These effects can impede the back diffusion of the hydrogen ion, enhance its neutralization and contribute to the prevention of mucosal damage and ulcers.

**c) Other proposed mechanisms for prostaglandin cytoprotection include:**
Enhancement of gastric mucosal blood flow, stimulation of DNA, RNA and protein synthesis (a doubtful mechanism for protection against acute gastric injury but it may encourage healing), stimulation of gastric mucosal cyclic AMP levels; stabilization of tissue lysosomal membranes, dissolution of gastric mucosal folds otherwise associated with hydrochloric acid and ethanol-induced gastric injury, maintenance of gastric mucosal folds otherwise associated with hydrochloric acid and other noxious water soluble agents. It seems doubtful that a single mechanism will explain the cytoprotective effects of all prostaglandins. Different types probably exhibit anti-ulcer activity by different mechanisms. The four synthetic prostaglandins currently undergoing clinical trials include Misoprostel (Searle), Arbaprostil (Upjohn).
Trimoprostil (Roche) and Enprostil (Syntex). They share a number of advantages, differences in comparison to the histamine H2 antagonists, antisecretory and cytoprotective actions, greater potency and relative lack of adverse effects and serious toxicity. Recently, a new prostaglandin Ro- 22-6923, developed by Hoffman La Roche Inc. has been shown to possess highly significant anti-ulcer, antisecretory and cytoprotective properties. Further studies on this compound are under progress (Kurata JH et al., 1985; 88).

1.8.5. Mucosal Protective Agents:
The dictum 'no acid- no ulcer' fostered the concept that effective reduction in gastric acid secretion was the rational basis of peptic ulcer therapy. However, it soon became apparent that increased acid secretion was seen in not more than 30-40% of duodenal ulcer patients and rarely in patients of gastric ulcer (Takashima M, et al., 2001). The proposition that peptic ulcer disease was induced by relative deficiency in the mucosal defense system, rather than increase in the offensive acid-pepsin factor, has led to a sustained quest for drugs which could restore or augment mucosal defense.

1.8.6. Essential fatty acids:
Arachidonic acid, the PG precursor, exerts mucosal protection and this forms the basis of putative use of essential fatty acids in ulcer therapy. Long term exposure to ethanol in rats and man, results in decreased arachidonic acid and linoleic acid levels in membrane lipids in several tissues and may contribute to gastroduodenal mucosal injury induced by it (Shea-Donahue T et al., 1986).

1.8.7. Sucralfate:
Sucralfate, a basic aluminium salt of sucrose octasulphate was initially proposed to enhance the mucus gel component of the mucus-bicarbonate barrier, provides an ideal physical barrier which can protect the ulcer site from offensive intraluminal
factors. Furthermore, it can also attenuate peptic activity by adsorption of the enzyme and its substrates (Hawkey CJ et al., 1987).

1.8.8. Carbenoxolone:
The first drug in this series was shown to be an effective antiulcer agent though it had no effect on gastric acid secretion. It was postulated that it augmented the mucosal defense and was termed a "cytoprotective agent".

1.8.9. Liquorice products:
Glycyrrhiza glabra has been used for many years for the treatment of peptic ulcer with the assumption that it exerts a demulcent effect over the ulcer crater and facilitates healing (Lam SK et al., 1985)

1.8.10. Antacids:
Aluminium containing antacids are known to stimulate mucosal PG synthesis in low doses not likely to exert significant antacid effect. Long term use of these antacids, in subantacid doses, have been shown to induce significant mucosal protection.

1.8.11. Sulphydryl compounds:
Intragastric administration of cysteamine or dimethylmaleate induces significant mucosal protection, which appears to be PG mediated, initial clinical studies are encouraging.

1.8.12. Bismuth salts:
Tripotassium dicitrate bismuthate, a colloidal bismuth preparation, was initially introduced as an improved version of bismuth subnitrate, a demulcent used to aid ulcer healing. Bismuth also inhibits the growth of H-pylori and may be of benefit in ulcer relapse (Goel RK, et al., 1982)
1.8.13. Natural products:
Vegetable banana (Musa paradisiaca), narikelkhand (Coconut) and Tamra bhasma (Copper preparation)(Panda PK et al., 1993) Abhra rasayana, Araucaria bidwillii, Vernonia lasiopus, Vernonia galamensis, Black Tea, Asparagus racemosus, Glycyrrhiza glabra, Centella asiatica, Nux vomica, Pongamia pinnata, Aegle marmelos, Emblica officanalis, Cauvery-100-Polyherbal formulation, UL-409, PHF, Rhinax- PHF, Shankha Bhasma (Pandit S et al., 2000).

1.9. FLAVONOIDS - ANTI ULCER ACTIVITY:
Flavonoids are a group of polyphenolic compounds, which are widely distributed throughout the plant kingdom. To date about 3000 varieties of flavonoids are known (Kuhnau J et al., 976). Many have low toxicity in mammals and some of them are widely used in medicine for maintenance of capillary integrity (Cesarone M et al., R1992). Flavonoids exhibit several biological effects such as antiinflammatory, anti hepatotoxic and anti-ulcer actions (Bors W et al., 1990)(Colerige Smith PO et al., 1980) Some recent reports have indicated that many flavonoids possess antiulcerogenic activity. Oral treatment with the ether fraction of the flavonoid extract demonstrated a good level of gastric protection. Mucous content was increased and accompanied by proportionate increase in proteins and hexosamines (Alarcon DLLC et al., 1994). β Hydroxy ethyl rutosides, gossypin, naringin, naringenin and (+)-Cyanidanol-3 were shown to exhibit anti-ulcer activity (Parmar NS et al., 1998). Quercetin, rutin and kaempferol administered intraperitoneally (25- 100 mg/kg) inhibited dose-dependent gastric damage produced by acidified ethanol in rats. Flavone was inactive while naringin was active at a higher dose (200 mg/kg). Quercetin, kaempferol, morin, myricetin and rutin when tested were found to inhibit the mucosal content of platelet activating factor (PAF) in a dose dependent manner suggesting that the protective role of these substances may be mediated by endogenous PAF (Parmar NS et al., 1998). Quercetin, kaempferol, rutin produced an inhibitory effect on intestinal functions, and that their actions are mediated through α2-adrenergic and calcium systems (IZZOA et al., 1994). This result may show the beneficial effects in diarrhea and other intestinal secretions. Lorenz et al (Lorenz W
et al., 1973). Showed that (+)-Cyanidanol-3 has histidine decarboxylase inhibitory activity and hence anti-ulcer activity (Lorenz W et al., 1973). 3-Methoxy-5,7,3',4'-tetrahydroxy flavan (Meciadanol), a congener of (+)-cyanidanol-3 exhibited significant anti-ulcer activity in pylorus ligated rats, restraint ulcers and gastric mucosal damage induced by aspirin models (Parmar NS et al., 1998)

1.10. Ethanol Induced Ulcers:
Ethanol treatment produces hemorrhagic lesions mainly in the glandular segment of the stomach mucosa (Bose et al., 2003). Alcohol causes cell and plasma membrane damage that result in increased membrane permeability leading to intracellular accumulation of sodium and water (Desai et al., 1997). It inturn leads to Ischemia. Ischemia weakens the gastric mucosal barrier and increases the acid back-diffusion predisposing the gastric mucosa to damage. After reperfusion, the reactive oxygen species (ROS) are generated from the xanthine-xanthine oxidase system and activated neutrophils, leading to tissue lipid peroxidation (LPO), which in combination with gastric secretion, this is also results in damage and cellular death (Rao et al., 2007) ROS are involved in the ethanol-induced mucosal damage leading to oxidative stress. In order to protect tissues against the damage provoked by ROS, all cells contain antioxidant enzymes, including glutathione peroxidase (GPx), Catalase (CAT), superoxide dismutase (SOD), glutathione reductase (GR) and radical scavengers, such as sulfhydryl compounds (GSH) (Farias-silva et al., 2007)
1.11. REVIEW OF LITERATURE:

*Acanthus ilicifolius* (Sea Holy)
1.11.1. Phytography:
Erect or rarely scandent perennial shrubs up to 2 m tall; stems several, stout, glabrous, base with stilt roots. Leaves glabrous, shining, 5-11 x 3-8 cm, various, usually ovate-oblong, elliptic or ovate-lanceolate, pinnatifid or toothed, rigid, narrowed at base, obtusely spinous at apex, marginal teeth spinous, nerves strong. Flowers in terminal spikes. Flowers sessile, 3.5-4 cm long, in terminal or pseudo-axillary densely strobilate spike; bracts 1-2 cm long, acute, ovate, glabrous; calyx 4 segmented, lobes glabrous, shortly connate in two opposite pairs; corolla 5 segmented, 3.4 cm long, blue or bluish violet, segments connate, 2 lipped, hairy outside; stamens with thick filaments, anthers densely bearded. Capsule ovoid-oblong, up to 3 cm long, compressed, apiculate, brown, shining. Seeds 4.
The species is easily recognisable in the field from its holy-like leaves and attractive bluish flowers. Gregarious along the tidal swamps in the sheltered mangrove areas, mostly as a secondary formation. Rarely seen in freshwater indicating its ecological amplitude and tolerance. Flowering and fruiting from April-August. They are considered as mangrove associates as they lack typical adaptations such as pneumatophores and vivipary.

1.11.2. Taxonomical Classification:

<table>
<thead>
<tr>
<th>Division</th>
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<tr>
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<td>Dicotyledonae</td>
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<tr>
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<td>Gamopetalae</td>
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<td>Bicarpellatae</td>
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<tr>
<td>Order</td>
<td>Personales</td>
</tr>
<tr>
<td>Family</td>
<td>Acanthaceae</td>
</tr>
<tr>
<td>Genus</td>
<td>Acanthus</td>
</tr>
<tr>
<td>Species</td>
<td>ilicifolius L.</td>
</tr>
</tbody>
</table>

Fig 14 Taxonomical Classification of the Acanthus ilicifolius

29
1.11.3. **Occurrence and Distribution:**
Mangroves of Indian peninsula; Sri Lanka, Bangladesh, Pakistan and the adjoining areas.

1.11.4. **Phenology:** Flowering and Fruiting: almost throughout the year.
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Introduction and Review of Literature

BIOGEOGRAPHICAL DISTRIBUTION OF ACANTHUS ILICIFOLIUS

Fig 16 Occurrence Distribution of Acanthus ilicifolius
1.11.5. Vernacular Names:

<table>
<thead>
<tr>
<th>Marandi (Marathi)</th>
<th>Aairtrumui</th>
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<tr>
<td>Alsi (Telugu)</td>
<td>Chulli</td>
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<tr>
<td>Akhi (Telugu)</td>
<td>Marandi</td>
</tr>
<tr>
<td>Sea Holly (English)</td>
<td>Kantali</td>
</tr>
<tr>
<td>Holly Mangrove (English)</td>
<td>Uppuchulli (Malayalam)</td>
</tr>
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<td>Haraguja</td>
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<td>Vayalchulli (Malayalam)</td>
</tr>
<tr>
<td>Hargoza (Hindi)</td>
<td>Marandi (Marathi)</td>
</tr>
</tbody>
</table>

Fig 17 Vernacular Names of Acanthus ilicifolius

1.11.6. Chemical Constituents:
acanthicifoline, oleanolic acid, β-sitosterol, lupeol, quercetin and its glucopyranoside, trigonellin; Root: saponin, glycoside of 3α-OH-lup-20(29)-ene. Aerial parts contain the alkaloids, acanthicifoline, oleanolic acid, β-sitosterol, lupeol, quercetin, its glucopyranoside and trigonelline. Roots contain triterpenoid, saponin and glycosides (Asolkar et al., 1992). Apigenin-7-O-glucuronide and a new flavone glycoside, methylapigenin-7-O- β-D-glucuronate has been isolated from the leaves (Ghani, 2003)
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1.11.7. Traditional Medicinal Uses of Plant Parts: (Mastaller, 1997)

Fruit pulp is used as a blood purifier and leaf paste in rheumatism. Fruit used in asthma, as aphrodisiac. Fruit, leaf, root are used to cure diabetes, diuretic, dyspepsia, hepatitis and leprosy. Bark, fruit, leaf are used to cure neuralgia, paralysis, ringworms, skin disease, stomach pains and snake bites. Local people use this plant to cure mumps. The leaves of this plant are made into paste and are applied to affected areas. Flowers of this plant are offered by teenage girls to kamadeva during pooram festival to get good spouses.

The Acanthus species are used in some countries to treat different diseases. Previous studies (Mastaller, 1997) have confirmed that some of the species produces compounds that exert some pharmacological activities, antimicrobial activities and anti-inflammatory agents. Isolated compounds from the plant material have been evaluated for both antimicrobial activities and anti-inflammatory activities (Geissberger and Sequin (1991). Cytotoxic efficacy of Acanthus ilicifolius (family of Acanthaceae) is a valuable medicinal plant that is widespread in tropical Asia and Africa, through Malaya to Polynesia (Xie et al., 2005). Acanthus ilicifolius extracts have been used in various folk medicines as remedies against rheumatism, neuralgia, poison arrow wounds, coughs, asthma and bacterial infections with subsequent scientific supports to these claims (Mastaller, 1997).

Malaysia: The leaves of A. ilicifolius are used to treat rheumatism, neuralgia and poison arrow wounds. It is widely believed among mangrove dwellers that chewing the leaves will protect against snake bite.

Malay: The pounded seeds of A. ilicifolius and A. ebracteatus are used to treat boils, and the juice of leaves to prevent alopecia. Both species are also used to treat urolithiasis.

India: In Ayurveda, the plant is known as Sahachara. According to Nadkarni the drug is astringent and makes a good nervine tonic, expectorant, and stimulant. He says that the root is expectorant, and is used in coughs and asthma. The root, boiled in milk, is largely used in leucorrhoea and general debility. Loureiro says that the Siamese and Indo-Chinese consider the roots to be cordial and attenuant, and useful
in paralysis and asthma. The tender shoots and leaves are used in India for bite. In Goa, the leaves, which abound in mucilage, are used as an emollient fomentation in rheumatism and neuralgia.

**Thailand:** Water extracted from the bark is used to treat colds and dermatitis. Ground fresh bark is used as an antiseptic. Tea brewed from the leaves relieves pain and purifies the blood.

**Modern use:** Plant: in asthma; Decoction of plant: in dyspepsia; Leaf and tender shoot: in snake bite; Root: in asthma, paralysis, leucorrhoea and debility; Leaf: as fomentation in rheumatism, neuralgia and in snake bite